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Request for grant of a Patent

Form 1/77 — **Patents Act 1977**

1 Title of invention

1 Please give the title of the invention

PHARMACEUTICAL FORMULATIONS

2 Applicant's details

☑ **First or only applicant**

2a If you are applying as a corporate body please give:

Corporate name
PFIZER LIMITED 6891267300 1

Country *(and State of incorporation, if appropriate)*
UNITED KINGDOM

2b If you are applying as an individual or one of a partnership please give in full:

Surname

Forenames

2c **In all cases,** please give the following detail :

Address
RAMSGATE ROAD
SANDWICH, KENT

UK postcode CT13 9NJ
(if applicable)

Country UNITED KINGDOM

ADP number
(If known)

2d, 2e and 2f:
If there are further applicants please provide details on a separate sheet of paper.

Second applicant (if any)

2d If you are applying as a corporate body please give:

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3
An address for service in the United Kingdom must be supplied.
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3 Address for service details

3a Have you appointed an agent to deal with your application?

Yes [X] No [ ] ⇨ *go to 3b*

⇩
Please give details below

Agent's name
J.R. HAYLES
Agent's address
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RAMSGATE ROAD
SANDWICH
KENT
Postcode CT13 9NJ

6409593002

Agent's ADP number

3b:
If you have appointed an agent, all correspondence concerning your application will be sent to the agent's United Kingdom address.

3b If you have not appointed an agent please give a name and address in the United Kingdom to which all correspondence will be sent:

Name

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4 Reference number

4 Agent's or applicant's reference number *(if applicable)* PCS10303JRH-PROV

5 Claiming an earlier application date

5 Are you claiming that this application be treated as having been filed on the date of filing of an earlier application?

Please mark correct box

Yes ☐ No ☒ ⇨ *go to 6*

⇩ *please give details below*

☐ number of earlier application or patent number

☐ filing date *(day month year)*

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15(4) (Divisional) ☐ 8(3) ☐ 12(6) ☐ : 7(4) ☐

6 Declaration of priority

6

If you are declaring priority from a PCT Application please enter 'PCT' as the country and enter the country code (for example, GB) as part of the application number.

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6 If you are declaring priority from previous application(s), please give:

Country of filing	Priority application number *(if known)*	Filing date *(day,month,year)*

7 *The answer must be 'No' if:*
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- *there is an inventor who is not an applicant, or*
- *any applicant is a corporate body.*

7 Inventorship

7 Are you (the applicant or applicants) the sol inventor or the joint invento s?

Please mark the correct box

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A statement of nventorship on Patents Form 7/77 will need be filed (see Rule 15).

8 *Please supply duplicates of claim(s), abstract, description and drawing(s).*

8 Checklist

8a Please fill in the number of sheets for e ch of the following types of document contained in this applicatio

Continuation sheets for thi: Patents Form 1/77	0		
Claim(s)	2	Description	9
Abstract	0	Drawing(s)	1

8b Which of the following documents also accompanies the application?

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Priority documents *(please state how many)*	
Translation(s) of Priority documents *(please state how many)*	
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Patents Form 9/77 - Preliminary Exami ation/Search	
Patents Form 10/77 - Request for Subst ntive Examination	

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9 Request

I/We request the grant of a patent on th basis of this application.

Please sign here ⇨ Signed James Hayles Date 23/10/1998
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Pharmaceutical formulations

This invention relates to controlled-release oral pharmaceutical formulations of cGMP PDE-5 inhibitors, and to methods of treatment involving them.

Controlled-release oral pharmaceutical formulations are known. Their purpose is to modify the rate of drug release, for example to produce a constant rate of release of a drug into the gastrointestinal tract of a patient, or to delay the release of a drug into the gastrointestinal tract of a patient (see 'Sustained and Controlled Release Drug Delivery Systems', pp 3-6, edited by J R Robinson, published by Marcel Dekker Inc).

Cyclic nucleotide phosphodiesterases (PDEs) are a family of enzymes that catalyse the degradation of cyclic nucleotides. Cyclic nucleotides, particularly cAMP (i.e. cyclic adenosine 3',5'-monophosphate), are important intracellular second messengers. PDEs are one cellular component that regulates the concentration of cyclic nucleotides. In recent years, at least seven PDE enzymes (such as PDE-1 - PDE-7) as well as many subtypes of these enzymes, have been defined based on substrate affinity and cofactor requirements (Beavo JA and Reifsnyder DH, Trends Pharmacol. Sci. 11:1 0 [1990]; Beavo J, in: Cyclic Nucleotide Phosphodiesterases: Structure, Regulation and Drug Action., Beavo J and Housley MD (Eds.). Wiley: Chichester, pp. 3-15 [1990]).

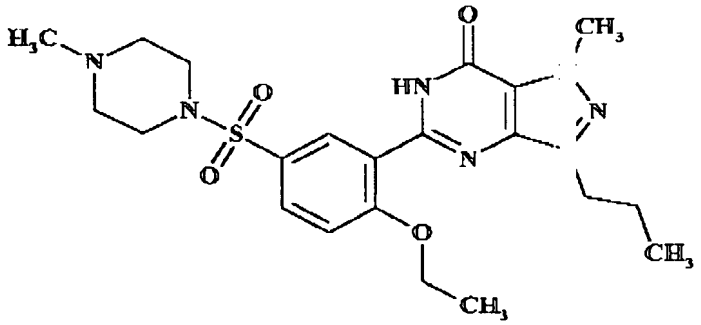
In slightly more detail, examples of PDEs (i.e. cyclic nucleotide phosphodiesterases) include: PDE-1 which is a Ca^{2+}/Calmodulin-dependent PDE; PDE-2 which is a cGMP stimulated PDE; PDE-3 which is a cGMP inhibited PDE; PDE-4 which is a high affinity cAMP-specific PDE; and PDE-5 which is a cGMP specific PDE.

It is believed that PDE-5 is an important enzyme in the physiological response to sexual stimulation, and that inhibitors of the enzyme are useful in the treatment of sexual dysfunction.

In males, sexual dysfunction may be defined as the inability to obtain or sustain a penile erection adequate for satisfactory sexual intercourse. In females, sexual dysfunction may

be defined as deficient physiological response to sexual s mulation and/or a deficient subjective feeling of arousal.

A PDE-5 inhibitor of particular interest is sildenafil {5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)phenyl]-1,6-dihydro-1-methyl-3-propyl yrazolo[4,3-d]pyrimidin-7-one}, which has the following structure:



The compound was first disclosed in European Patent Appli ation 463756, and its use in the treatment of sexual dysfunction was disclosed in Internat onal Patent Application WO 94/28902. A formulation of the citrate salt (VIAGRA™) was made available for the treatment of male erectile dysfunction in a number of countrie including the USA in 1998. VIAGRA™ is an immediate release tablet that is adminis red about 1 hour before an effect is required, and the duration of action is about 4 hours.

The main interest in the art so far has been to provide a fa t-acting treatment of sexual dysfunction, which can be administered as soon as possible before sexual activity. For example, International Patent Application WO 98/30209 discloses a rapidly releasing formulation of sildenafil citrate.

According to the present invention, there is provided a conti olled-release formulation for oral administration containing a cGMP PDE-5 inhibitor.

Usually, formulations according to the invention will be ablets or capsules that are swallowed. However, the invention also includes buccal ormulations (which may be tablets, ointments, gels or patches).

Controlled-release formulations may be divided into susta ied-release and delayed- or pulsatile- release formulations.

Sustained-release dosage forms release their active ingredient into the gastro-intestinal tract of a patient over a sustained period of time following administration of the dosage form to the patient. Particular dosage forms include:

(a) those in which the active ingredient is embedded in a matrix from which it is released by diffusion or erosion;
(b) those in which the active ingredient is present in or on a multiparticulate core which is coated with a rate controlling membrane;
(c) those in which the active ingredient is present in a dosage form having a coating impermeable to the drug, and release is via a drilled aperture;
(d) those in which the active ingredient is released through a semi permeable membrane, allowing the drug to diffuse across the membrane or through liquid filled pores within the membrane; and
(e) those in which the active ingredient is present as an ion exchange complex.

It will be apparent to those skilled in the art that some of the above means of achieving sustained-release may be combined, for example a matrix containing the active compound may be formed into a multiparticulate and/or coated with an impermeable coating provided with an aperture.

Pulsed-release formulations release the active compound after a sustained period of time following administration of the dosage form to the patient. The release may then be in the form of immediate- or sustained-release. This delay may be achieved by releasing the drug at particular points in the gastro-intestinal tract or by releasing drug after a pre-determined time. Pulsed-release formulations may be in the form of tablets or multiparticulates or a combination of both. Particular dosage forms include:

(a) osmotic potential triggered release (see US patent no 3,9[illegible],741);
(b) compression coated two layer tablets (see US patent no. 5,464,633);
(c) capsules containing an erodible plug (see US patent no 5,[illegible]74,784);
(d) sigmoidal releasing pellets (referred to in US patent no 5,[illegible]12,621); and
(e) formulations coated with or containing pH-dependent polymers including shellac, phthalate derivatives, polyacrylic acid derivatives and crotonic acid copolymers.

Dual release formulations can combine the active ingredie t in immediate release form with additional active ingredient in sustained release form. For example a bilayer tablet can be formed with one layer containing immediate release a ctive ingredient and the other layer containing the active ingredient embedded in a matrix from which it is released by diffusion or erosion. Dual release formulations can also combine drug in immediate release form with additional drug in pulsed release for t. For example a capsule containing an erodible plug could liberate drug initially and a ter a predetermined period of time further drug in immediate- or sustained-release form.

Preferably, formulations according to the present inv ntion are sustained-release formulations. For example, it is preferred that up to 75% by eight of the active ingredient is released from the formulation in the GI tract (or in a model of the GI tract) in a period 1-24 hours following administration, for example 6-18 hours.

An advantage of sustained-release formulations according to he present invention is that a patient receiving them would have improved sexual function or a sustained period of time following administration (such as 6-24 hours, for example 1 2-18 hours), and so be ready for sexual activity at almost any time. This would allow a m re spontaneous sex-life to be pursued.

In addition, it is thought that in male patients at risk of devel ping sexual dysfunction (for example diabetic patients or patients having underg ne nerve sparing radical prostatectomy), the prevalence of nocturnal erections is dim nished. Nocturnal erections may play an important role in preserving normal erectile f nction by providing regular tissue oxygenation thus preventing tissue fibrosis and erectile degeneration. Thus, a cGMP PDE-5 inhibitor delivered to a patient during sleep will i crease the ability of at-risk individuals to have nocturnal erections, increase tissue oxyge ation, prevent penile fibrosis and thus preserve erectile function or slow its decline. Dela ed release formulations may be of particular use in this instance, providing PDE-5 inhib tion throughout the sleeping period.

A further advantage of formulations according to the presen invention is that side effects may be reduced. For example, although sildenafil offers a safe, effective and generally

very well tolerated oral treatment for male erectile dysfunctio , dose-related reversible side effects such as headache or visual disturbance at high do age may limit its use in a minority of patients. Such effects are mediated by sys mic exposure to sildenafil following oral administration: thus a formulation with a su ained release profile, which avoids initial high plasma concentrations, could be of great va ue to these patients.

Preferably, the cGMP PDE-5 inhibitor is sildenafil, or a pha maceutically acceptable salt thereof (such as the citrate salt).

Other cGMP PDE-5 inhibitors (previously mentioned in WO 94/28902) that may be mentioned include:
5-(2-ethoxy-5-morpholinoacetylphenyl)-1-methyl-3-n-propyl- 1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (UK-114,542);
5-(5-morpholinoacetyl-2-n-propoxyphenyl)-1-methyl-3-n-pro yl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-[2-allyloxy-5-(4-methyl-1-piperazinylsulphonyl)phenyl]-1- ethyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-{2-ethoxy-5-[4-(2-propyl)-1-piperazinylsulphonyl]phenyl}- -methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-{2-ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl]pl enyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-{5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl]-2-n-propo yphenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-[2-ethoxy-5-(4-methyl-1-piperazinylcarbonyl)phenyl]-1-me hyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one; and
5-[2-ethoxy-5-(1-methyl-2-imidazolyl)phenyl]-1-methyl-3-n- ropyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

The following cGMP PDE-5 inhibitors (previously men ioned in WO 97/03675 to Laboratoire Glaxo Wellcome SA) may also be mentioned:
(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methyl nedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione; and
(3S,6R,12aR)-2,3,6,7,12,12a-hexahydro-2,3-dimethyl-6-(3,4- nethylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione.

Preferably, the formulation is a matrix tablet, and contains h droxypropylmethyl cellulose. Preferably, the hydroxypropylmethyl cellulose has a numbe average molecular weight in the range 80,000-250,000. Preferably, the hydroxypropylm hyl cellulose has a degree of methyl substitution in the range 19-30%. Preferably, the h droxypropylmethyl cellulose has a degree of hydroxy substitution in the rang 7-12%. A number of hydroxypropylmethyl cellulose polymers are available comm rcially under the brand name Methocel™, and some of those suitable for use in formulati ns according to the invention are given in the table below:

Methocel™ grade	Number average MW	Degree of methyl substitution	Degree of hydroxy substitution	Nominal viscosity of a 2% aqueous solution	USP designation
K4M	89000	19-24%	7-12%	4000cps	2208
K15M	125000	"	"	15000cps	"
K100M	215000	"	"	100000cps	"
E4M	93000	28-30%	7-12%	4000cps	2910
E10M	113000	"	"	10000cps	"
F4M	90000	27-30%	4-7.5%	4000cps	2906

Methocel™ K4M has characteristics of particular interest.

It will be apparent to those skilled in the art that the hydro ypropylmethyl cellulose may consist of molecules of different chain lengths, but that the average chain length gives a molecular weight in the range stated.

Formulations according to the present invention may conta a buffering agent. This is particularly useful when the formulation contains sildenafil citrate. A buffering agent of particular interest is aspartic acid. When it forms part of a m atrix tablet, aspartic acid acts as a buffering agent to maintain a low pH at the surface of he tablet. Because sildenafil citrate has a low solubility at pH values greater than 6, the cid keeps the drug relatively soluble during the transit of the tablet through the GI tract. When present, aspartic acid will typically make up 15-30% by weight of the formulation.

Usually, the formulations of the present invention will include tabletting excipients, for example colloidal anhydrous silica, polyvinylpyrrolidone, lactose and magnesium stearate. Lactose is of particular interest, and when present it will typically make up 10-40% by weight of the formulation.

Formulations according to the invention may be provided additionally with a cosmetic coating; for example a coating comprising a pigment, a plasticizer and a polymer such as OPADRY™ (manufactured by Colorcon), or a sugar coating. Such coatings do not substantially affect the performance of the formulation, but enhance its presentation. Such coatings may be applied by spraying tablet cores with a solution of the components, using conventional techniques.

Preferably, in formulations according to the present invention, the cGMP PDE-5 inhibitor makes up 5-50% by weight of the formulation.

Preferably, in formulations according to the present invention, the hydroxypropylmethyl cellulose makes up 10-50% by weight of the formulation.

Preferably, in formulations according to the present invention, the rate at which the cGMP PDE-5 inhibitor is released therefrom is substantially independent of the pH of the surroundings.

The present invention also provides a process for the production of a pharmaceutical formulation containing hydroxypropylmethyl cellulose, which includes the steps of mixing the cGMP PDE-5 inhibitor and hydroxypropylmethyl cellulose; and pressing into tablets.

The invention further provides the use of a cGMP PDE-5 inhibitor in the manufacture of a formulation for the treatment or prevention of sexual dysfunction; characterized in that, following administration, the formulation releases the inhibitor over or after a sustained period of time. Consequently, following administration, the mammal's sexual function will be substantially improved for or after a sustained period of time.

Usually, the mammal will be a human, but administration to other mammals, such as horses, is contemplated.

A "sustained period of time" in relation to the improvement a sexual function is a period of time such as 6-24 hours, for example 12-18 hours.

The invention further provides a method of treating or preventing sexual dysfunction, which comprises administering a controlled-release formulation of a cGMP PDE-5 inhibitor to a mammal in need of such treatment or prevention. Consequently, the mammal's sexual function is substantially improved for or after a sustained period of time.

The invention further provides a method of improving sexual function in a mammal, which comprises administering a sustained-release formulation of a cGMP PDE-5 inhibitor to the mammal. Consequently, the mammal's sexual function is substantially improved for a sustained period of time.

The invention is illustrated by the following examples with reference to the accompanying drawing, in which Figure 1 shows the percentage of drug compound released v time from a formulation prepared according to Example 1 under three different pH conditions.

Example 1

Sustained release formulation of sildenafil citrate

Component	Weight per 450mg matrix tablet (mg)
Sildenafil citrate (69.1% Activity)	144.72
L-Aspartic acid	100
Methocel™ grade K4M	67.5 (15%)
Lactose Fast-flow	133.28
Magnesium Stearate	4.5

Method

1. Blend components, less magnesium stearate, for 10 minutes in a turbula
2. Screen through a 500µm sieve

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3. Add 26% water (by weight) with blending
4. Screen through a 1.7mm sieve
5. Dry resulting granules in a vacuum oven at 40°C, 207 kPa (300 psi) until the moisture level is returned to original value
6. Screen through a 1.0mm sieve
7. Add magnesium stearate and blend for 5 minutes
8. Press into tablets using 11mm normal concave tablet t oling

Example 2

Dissolution studies

Formulations prepared in Example 1 were dissolved using Apparatus 1 (baskets) described in United States Pharmacopeia 23 (1995), page 1791, in an aqueous buffer of pH 2 (composition 0.01M HCl and 0.12M NaCl), an aqueous buffer of pH 4.5 (composition 0.06M KCl, 0.03M NaCl and 0.006M KH_2PO_4) and in an aqueous buffer of pH 7.5 (composition 0.06M KCl, 0.03M NaCl, 0.006M KH_2PO_4 and 0.005M NaOH). The dissolution fluid volume was 1 l in the case of pH 2 and pH 4.5, but 5 l in the case of pH 7.5 (also replaced periodically), the temperature was 37°C, the rotation speed of the baskets was 100 rpm, and the drug compound released was detected by UV spectroscopy. The percentage of drug compound released v time is shown in Figure 1.

It can be seen that the release profiles at the three pH values are almost identical, indicating that the formulation is likely to give a steady, sustained rate of release of drug over a sustained period of time when administered orally to a patient

Claims:

1. A controlled-release formulation for oral administrati n containing a cGMP PDE-5 inhibitor.

2. A formulation as claimed in claim 1, which is a sustai ed-release formulation.

3. A formulation as claimed in claim 1 or claim 2, wher n the cGMP PDE-5 inhibitor is sildenafil, or a pharmaceutically acceptable salt thereof.

4. A formulation as claimed in any one of the prec ling claims, which contains sildenafil citrate.

5. A formulation as claimed in any one of the precedin claims, which also contains hydroxypropylmethyl cellulose.

6. A formulation as claimed in any one of the preceding laims, which also contains a buffering agent.

7. A formulation as claimed in claim 5 or claim 6, whe in the hydroxypropylmethyl cellulose has a number average molecular weight in the range 30,000-250,000.

8. A formulation as claimed in any one of cla ns 5 to 7, wherein the hydroxypropylmethyl cellulose has a degree of methyl substit tion in the range 19-30%.

9. A formulation as claimed in any one of cla ns 5 to 8, wherein the hydroxypropylmethyl cellulose has a degree of hydroxy subst ution in the range 7-12%.

10. A formulation as claimed in any one of the precedi g claims, which is provided with a cosmetic coating.

11. A formulation as claimed in any one of the precedin claims, wherein the cGMP PDE-5 inhibitor makes up 5-50% by weight of the formulatio .

12. A formulation as claimed in any one of clai s 5 to 11, wherein the hydroxypropylmethyl cellulose makes up 10-50% by weight the formulation.

13. A formulation as claimed in claim 4, characterized that the rate at which the cGMP PDE-5 inhibitor is released therefrom is substantially ndependent of the pH of the surroundings.

14. A process for the production of a formulation as defin d in claim 5, which includes the steps of mixing the cGMP PDE-5 inhibitor and hydrox propylmethyl cellulose; and pressing into tablets.

15. Use of a cGMP PDE-5 inhibitor in the manufact e of a formulation for the treatment or prevention of sexual dysfunction; chara erized in that, following

administration, the formulation releases the inhibitor over a · after a sustained period of time.

16. The use of claim 15, characterized in that, following a dministration, the mammal's sexual function is substantially improved for or after a sustain d period of time.

17. A method of treating or preventing sexual dy function, which comprises administering a controlled-release formulation of a cGMP PI E-5 inhibitor to a mammal in need of such treatment or prevention.

18. The method of claim 17, characterized in that, f llowing administration, the mammal's sexual function is substantially improved for or aft r a sustained period of time.

19. A method of improving sexual function in a nammal, which comprises administering a sustained-release formulation of a cGMP PDI -5 inhibitor to the mammal.

20. The method of claim 19, characterized in that, f llowing administration, the mammal's sexual function is substantially improved for sustained period of time.

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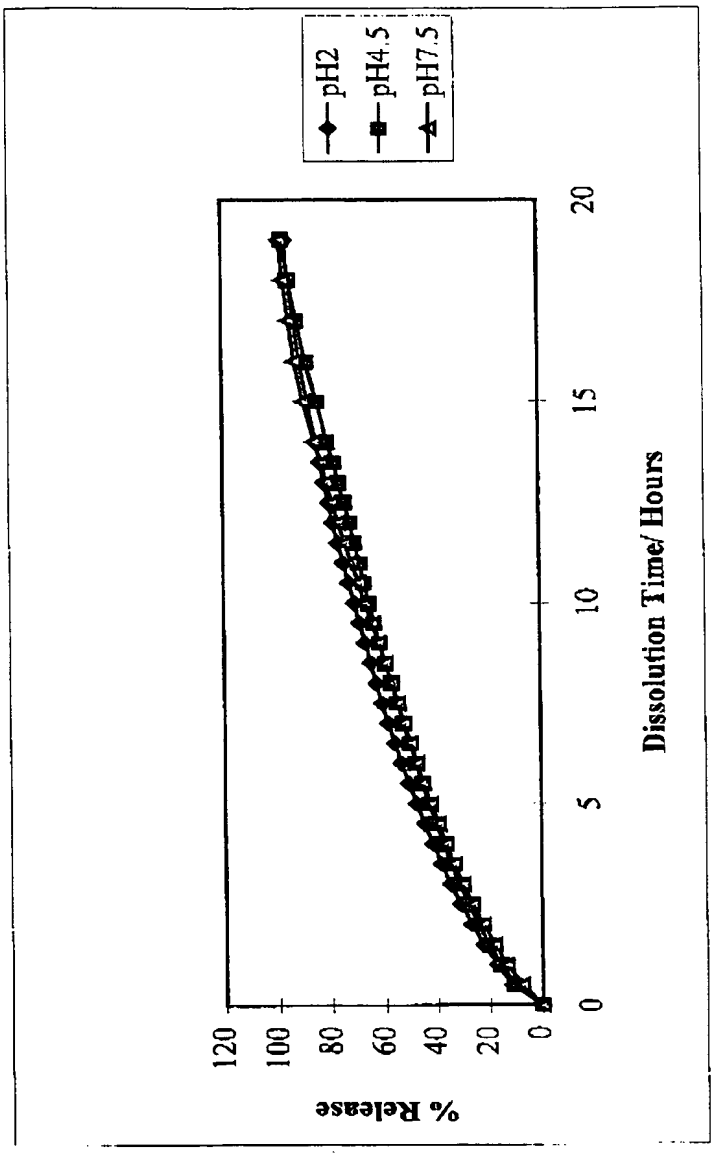

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